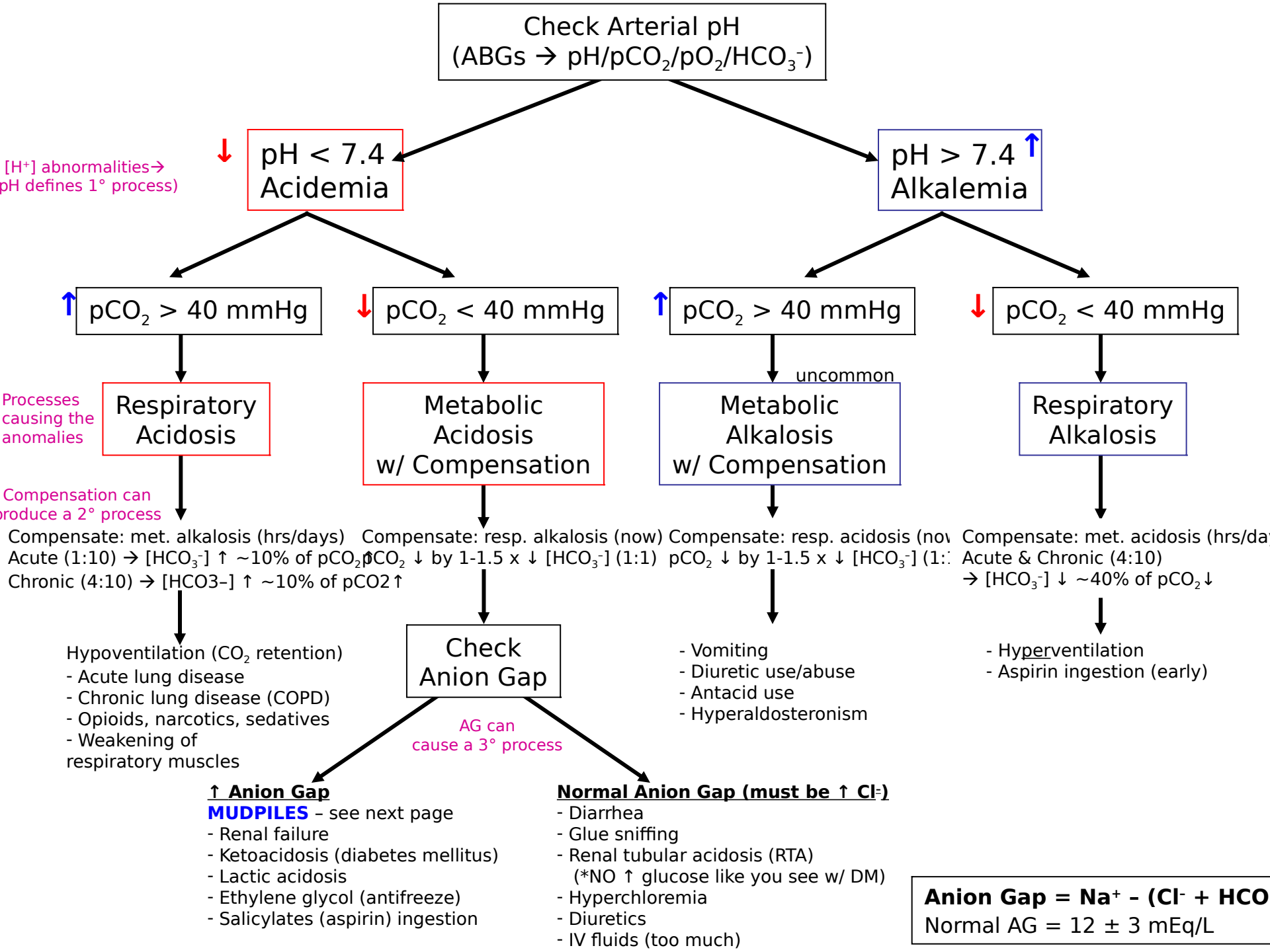
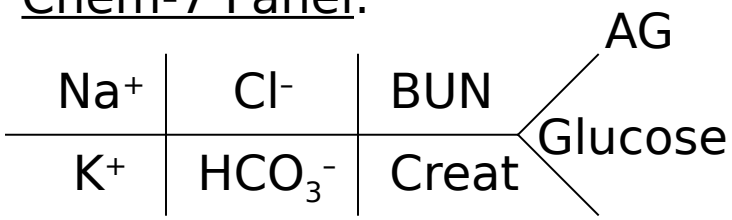
Clinical Concepts


Check Arterial pH
(ABGs → pH/pCO2/pO2/HCO3-)
[H+] abnormalities→
pH defines 1° process)
pH < 7.4
Acidemia
pH > 7.4
Alkalemia
pCO2 > 40 mmHg
pCO2 < 40 mmHg
pCO2 > 40 mmHg
pCO2 < 40 mmHg
uncommon
Processes
causing the
anomalies
Respiratory
Acidosis
Metabolic
Acidosis
w/ Compensation
Metabolic
Alkalosis
w/ Compensation
Respiratory
Alkalosis
Compensation can
produce a 2° process
Compensate: met. alkalosis (hrs/days)
Acute (1:10) → [HCO3-] ↑ ~10% of pCO2↑
Chronic (4:10) → [HCO3–] ↑ ~10% of pCO2↑
Compensate: resp. alkalosis (now)
pCO2 ↓ by 1-1.5 x ↓ [HCO3-] (1:1)
Compensate: resp. acidosis (nov
pCO2 ↓ by 1-1.5 x ↓ [HCO3-] (1:
Compensate: met. acidosis (hrs/da
Acute & Chronic (4:10)
→ [HCO3-] ↓ ~40% of pCO2↓
Hypoventilation (CO2 retention)
- Acute lung disease
- Chronic lung disease (COPD)
- Opioids, narcotics, sedatives
- Weakening of
respiratory muscles
Check
Anion Gap
- Vomiting
- Diuretic use/abuse
- Antacid use
- Hyperaldosteronism
- Hyperventilation
- Aspirin ingestion (early)
AG can
cause a 3° process
↑ Anion Gap
MUDPILES – see next page
- Renal failure
- Ketoacidosis (diabetes mellitus)
- Lactic acidosis
- Ethylene glycol (antifreeze)
- Salicylates (aspirin) ingestion
Normal Anion Gap (must be ↑ Cl-)
- Diarrhea
- Glue sniffing
- Renal tubular acidosis (RTA)
(*NO ↑ glucose like you see w/ DM)
- Hyperchloremia
- Diuretics
- IV fluids (too much)
Anion Gap = Na+ – (Cl- + HCO
Normal AG = 12 ± 3 mEq/L

Anion Gap = Na^+ – (Cl^- + HCO_3^-)
Normal AG = 12 ± 3 mEq/L

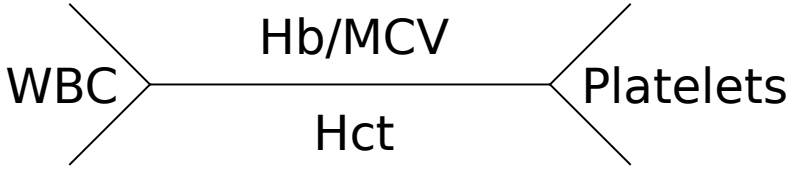
Chem-7 Panel:



Elevation in Anion Gap due to: [MUDPILES]

- **M**ethanol
- **U**remia (chronic renal failure)
- **D**iabetic ketoacidosis
- **P**araldehyde or **P**henoformin
- **I**ron tablets or **I**NH
- **L**actic acidosis (CN^-, CO, shock)
- **E**thanol or Ethylene glycol (antifreeze)
- **S**alicylate (aspirin)

Blood Panel:



Remember that in PRIMARY respiratory acid-base disorders, the deflection of pH & pCO_2 is in OPPOSITE directions!
So the next question is, acute vs. chronic? The answer lies in the normality of the pH relative to the derangement i
To achieve this, sufficient time must pass to allow the kidney to compensate for the primary disorder (hypocapnia)
by excreting bicarbonate in the urine. Chronically, for every decrement of 10 mmHg pCO_2, we expect a compensat
decrement in bicarbonate of about 5 mmol/L (assume a normal starting bicarbonate concentration of 24 mmol/L).
compensation is NOT appropriate, there must be another process (or processes!) occurring simultaneously (mixed

Signs of mixed disorders:
- Marked increase in pH with little change in pCO_2 & [HCO_3^-]
- Marked increase in pCO_2 & [HCO_3^-] with little change in pH → offsetting abnormality

Simplified analysis of the excess anion gap (AG) [also called delta-delta analysis]:
- ΔAG = calculated AG – 12
- Δ[HCO_3^-] = 24 – measured [HCO_3^-]
- Compare the two → ΔAG > Δ[HCO_3^-] = metabolic alkalosis + metabolic acidosis
- → ΔAG < Δ[HCO_3^-] = wide AG + non-AG metabolic acidosis
- → ~Equal? = wide anion gap metabolic acidosis
- NO anion gap → non-anion gap metabolic acidosis (aka. hyperchloremic acidosis); think about it…if you have met
acidosis with no anion gap, the only serum anion that can be causing it is chlorine

A 20 year old Marine presents for Emergency Room care with new-onset type 1 diabetes mellitus accom
three-day history of anorexia, nausea, and vomiting. His vital signs include temperature 100 degrees F,
80/50 sitting; pulse 90 supine, 130 sitting, respirations 24/minute. On urinalysis dipstick, he has "large"
ketones, and he has serum electrolytes as follows: sodium, 136 mEq/L; potassium, 5.3 mEq/L; chloride 9
bicarbonate, 14 mEq/L; glucose 424 mg/dl; BUN, 30 mg/dl; creatinine, 1.0 mg/dl.
His arterial pH is 7.32; pCO2 is 28 mmHg; pO2 is 98 mmHg.
Which of the following most completely describes his acid-base abnormality?

Chronic respiratory alkalosis
Wide anion gap metabolic acidosis
Mixed anion gap metabolic acidosis and metabolic alkalosis
Mixed respiratory alkalosis and wide anion gap metabolic acidosis
Mixed respiratory alkalosis, wide anion gap metabolic acidosis, and metabolic alkalosis

Answer: *Mixed anion gap metabolic acidosis and metabolic alkalosis*

You know you have to have a minimum diagnosis of metabolic acidosis, based on an acidemic pH and concurren
reflecting a trend towards compensation. Next step would be to apply a rule of compensation to see if the pCO2
for compensation; in this case, for metabolic acidosis, the rule is pCO2 = 1.5 x [HCO3] + 8 + 2; the observed va
is within this range, so there is no primary respiratory disorder. Next, we want to see if we can explain the meta
as simple metabolic acidosis. If so, it will be either a non-anion gap (a.k.a. hyperchloremic acidosis) metabolic a
wide anion gap acidosis. We then want to look at the anion gap, which is: [sodium] - ([chloride] + [bicarbonate]
the anion gap is 28, well above the normal anion gap of 12. So, we have at least a wide anion gap metabolic ac
But, is that all? We then compare the "delta" anion gap with the "delta" bicarbonate concentration: in a simple
acidosis, "delta" gap = "delta" bicarb. In this case, "delta" gap = 28 (observed) - 12 (normal), or 16.
"Delta" bicarb = 24 (normal) - 14 (observed), or 10. Since "delta" gap is greater than "delta" bicarb, there has t
else going on, and the most usual thing would be concurrent metabolic alkalosis--in this case, plasma volume c
vomiting are likely explanations. Clinical clues to volume contraction include orthostatic BP and pulse, the histo
reduced oral intake, and the increased insensible fluid loss obligated by glycosuria-induced osmotic diuresis.

A 27 year old Staff Sergeant presents to sick call with a two-day history of nausea and vomiting. Her tem
100.4 degrees F; BP is 100/60 supine and 80/50 sitting; pulse is 100 supine and 130 sitting. Her examinat
only remarkable for mild epigastric tenderness and decreased bowel sounds. Serum electrolytes are sodi
potassium, 3.2 mEq/L; chloride, 90 mEq/L; bicarbonate 32 mEq/L; BUN, 24 mg/dl; creatinine, 0.5 mg/dl; gl
Urine electrolytes are sodium, < 10 mEq/L; and chloride, < 10 mEq/L.
An arterial blood gas shows pH 7.47; pCO2 45 mmHg; pO2 98 mmHg.
What acid-base disturbance is present?

Chronic respiratory acidosis
Metabolic alkalosis
Mixed non-anion gap metabolic acidosis and metabolic alkalosis
Mixed respiratory acidosis and metabolic alkalosis
Mixed respiratory acidosis, non-anion gap metabolic acidosis, and metabolic alkalosis

Answer: ***Metabolic alkalosis***

The minimum diagnosis has to be metabolic alkalosis, based on alkalemic pH and concurrent hypercarbia (i.e., p
both INCREASED). Is the hypercarbia of an appropriate degree? The pertinent rule of compensation is that for ev
in plasma bicarbonate, pCO2 should rise by 6 mmHg. In this case, the bicarbonate is up 8 mmol/L and the pCO2
normally say "close enough for government work" (and this is government work, after all!) The anion gap is 12, v
The low urine chloride is appropriate renal conservation reflecting loss of gastric acid from vomiting. So basically
a simple metabolic alkalosis! Note that again, the clinical history SUGGESTS the acid-base disturbance you confi

A 25 year old Marine is transferred to your hospital after suffering extensive crush wounds and fractures extremities in a battlefield simulation exercise. On arrival, he has a temperature of 101 degrees F, BP 140 120/70 semi-upright; pulse 70 supine and 90 upright; respirations 24/minute. His arterial blood gas revea pCO2 30 mmHg; pO2 65 mmHg. Serum electrolytes include sodium, 136 mEq/L; potassium, 5.3 mEq/L; chl bicarbonate, 18 mEq/L; BUN, 112 mg/dl; creatinine, 10.4 mg/dl; and glucose, 90 mg/dl.
What acid-base disturbance is present in this patient?

None--normal arterial pH rules out an acid-base disorder
Chronic respiratory alkalosis
Mixed respiratory alkalosis and wide anion gap metabolic acidosis
Mixed respiratory alkalosis, wide anion gap metabolic acidosis, and non-anion gap metabolic acidosis
Mixed respiratory alkalosis, wide anion gap metabolic acidosis, and metabolic alkalosis

Answer: ***Mixed respiratory alkalosis, wide anion gap metabolic acidosis, and metabolic alkalosis***

Apply our simplified approach sequentially, and you can master even the dreaded triple acid base disturbance! A is that the pH is normal even though there is significant hypocapnia; this finding should ALWAYS alert you to the "offsetting" metabolic and respiratory primary disorders. Sho' 'nuff, from the bicarbonate of 18, you would expect should be in the range of 33-37 mmHg; since it's lower, there has to be a respiratory alkalosis. The anion gap is 2 there HAS to be a metabolic acidosis of a wide anion gap variety (in this case, lactic and renal failure acidoses wo "Delta" gap = 12, in this case, but "delta" bicarbonate is only 6 (normal 24- observed 18). As before, when "delta" gap > "delta" bicarbonate, co-existing metabolic alkalosis and wide anion gap metabolic acidosis is the ru And note that again, vital signs suggest volume depletion due to the "tilt" in pulse and blood pressure when com and upright postures.

A 45 year old Navy Commander with a history of type 2 diabetes mellitus (non-insulin dependent) presen
Primary Care with a 2-day history of nausea, vomiting, and poor oral intake. In the clinic, he has orthosta
BP and pulse, an otherwise "non-focal" physical exam, and has 4+ glucose and ketones on a dipstick urin
An ABG is as follows: pH 7.55, pCO2 20 mmHg, pO2 90 mmHg, and bicarbonate 14 mEq/L.
Which of the following acid-base disturbances is present?

Acute respiratory alkalosis
Metabolic acidosis
Mixed respiratory alkalosis and metabolic acidosis
Mixed respiratory alkalosis, metabolic acidosis, and metabolic alkalosis
Undetermined acid-base abnormality due to laboratory/calculation error

Answer: *Undetermined acid-base abnormality due to laboratory/calculation error*

You should always make sure data are internally consistent before going through a lot of tortured machinations! the derived formula from the Henderson-Hasselback equation to calculate the [H^+] concentration: [H^+] = (24 x p then consult a chart to translate [H^+] into pH. In this case, [H^+] = 34 nEq/L, which corresponds with a pH of abou the given numbers has to be wrong. In real life, this calculation is done for you by reporting of a calculated bicar blood gas report. This value should be within 2 mmol/L of measured serum bicarbonate--if not, don't waste time

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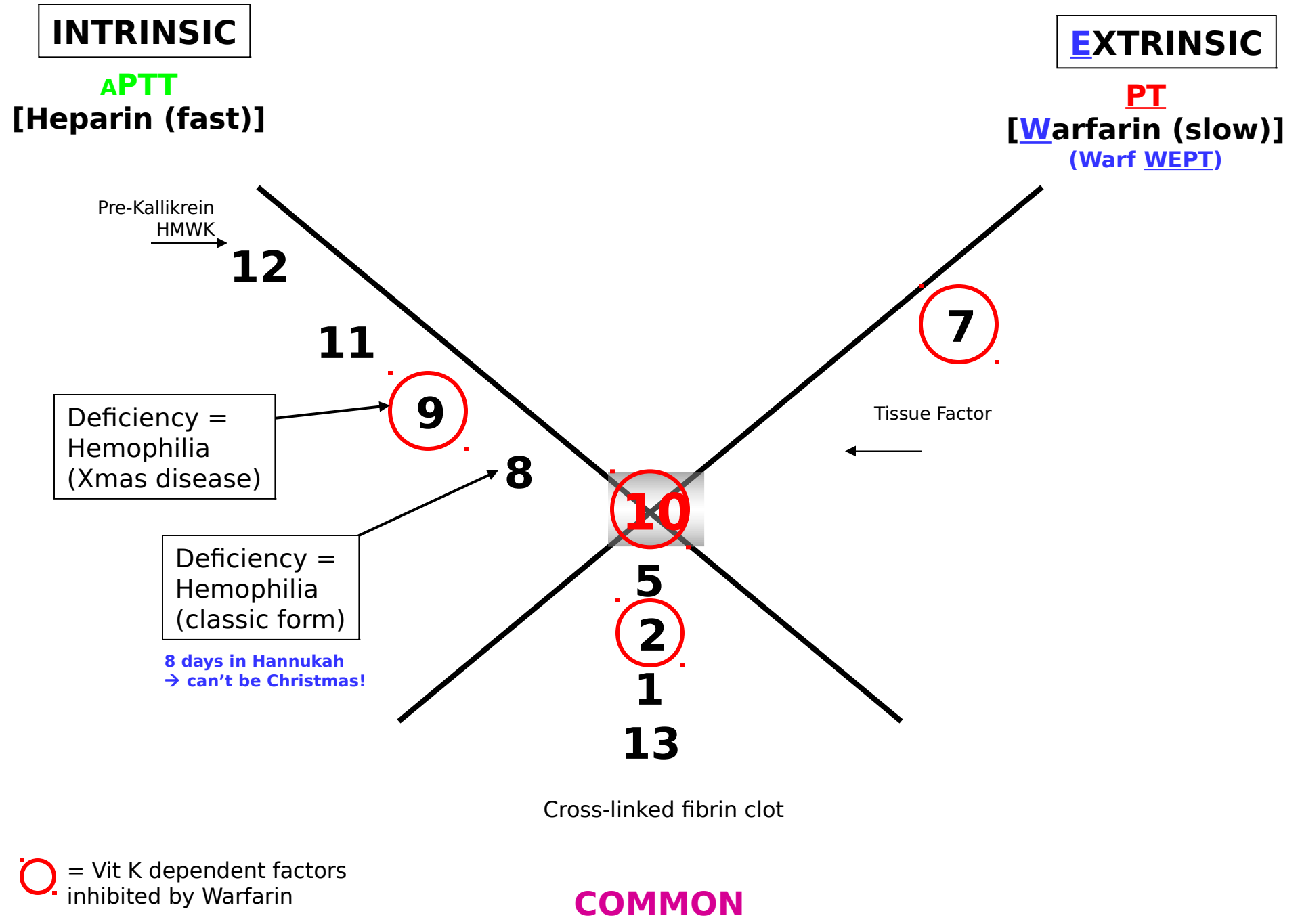
A 25 year old female Airman complains of chest tightness and lightheadedness and comes to the ER for e
appears to be very anxious, and has BP 110/70, pulse 90, and respiratory rate 20. Her lungs sound clear
EKG and chest x-ray are normal. Her arterial blood gas is as follows: pH 7.44, pCO2 25 mm Hg, pO2 98 mg
bicarbonate 17 mEq/L. What acid-base abnormality does she exhibit?

Acute respiratory acidosis
Chronic respiratory acidosis
Acute respiratory alkalosis
Chronic respiratory alkalosis
Mixed respiratory alkalosis and metabolic acidosis

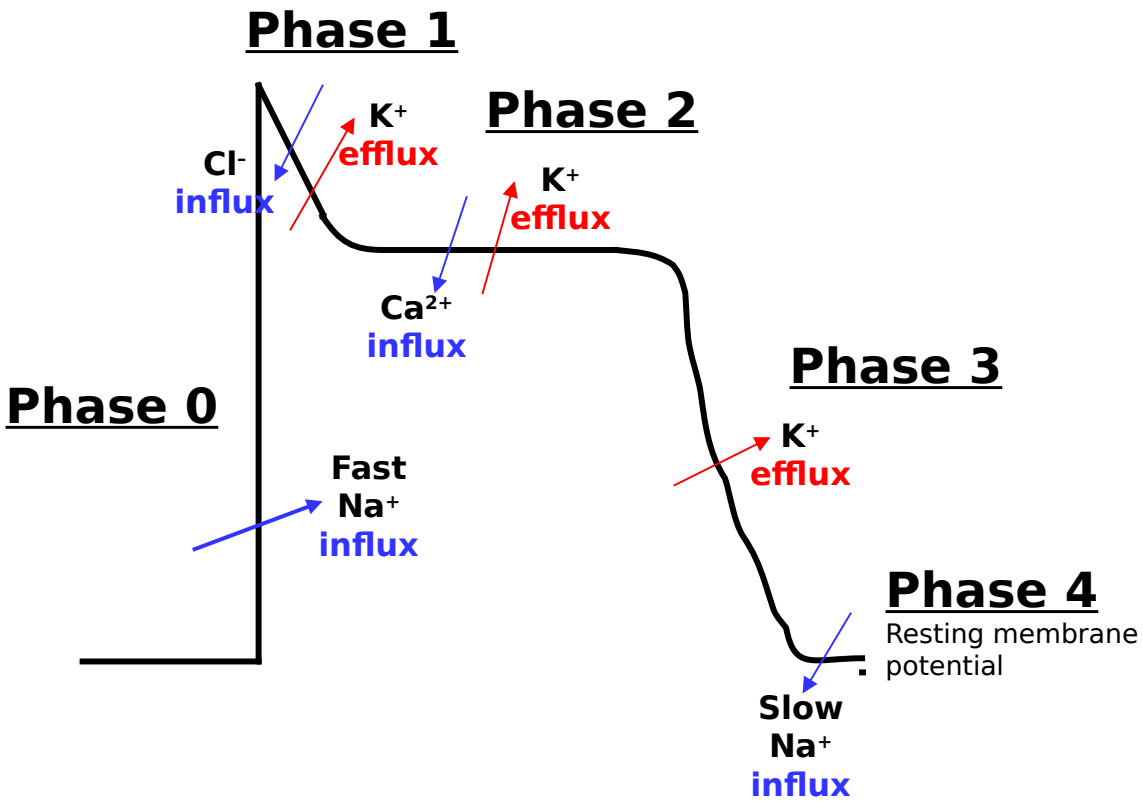
Answer: *Chronic respiratory alkalosis*

The patient has symptoms suggestive of hypocapnia--chest tightness & lightheadedness; she might also describ (tingling) involving her fingers, toes, & perioral region. You would suspect primary respiratory alkalosis, & indeed (alkalemic), while her pCO_2 is decreased. Remember, in PRIMARY respiratory acid-base disorders, the deflection OPPOSITE directions! So now the question is, acute vs. chronic? The answer lies in the normality of pH relative t pCO_2. To achieve this, sufficient time must pass to allow the kidney to compensate for the primary disorder (hyp excreting bicarbonate in urine. Chronically, for every decrement of 10 mmHg pCO_2, we expect a compensating d bicarbonate of ~5 mmol/L--which fits in this case, if you assume normal starting bicarbonate concentration of 24


INTRINSIC
aPTT
[Heparin (fast)]
EXTRINSIC
PT
[Warfarin (slow)]
(Warf WEPT)
Pre-Kallikrein
HMWK
12
11
9
Deficiency = Hemophilia (Xmas disease)
8
Deficiency = Hemophilia (classic form)
8 days in Hannukah
→ can't be Christmas!
7
Tissue Factor
10
5
2
1
13
Cross-linked fibrin clot
= Vit K dependent factors inhibited by Warfarin
COMMON

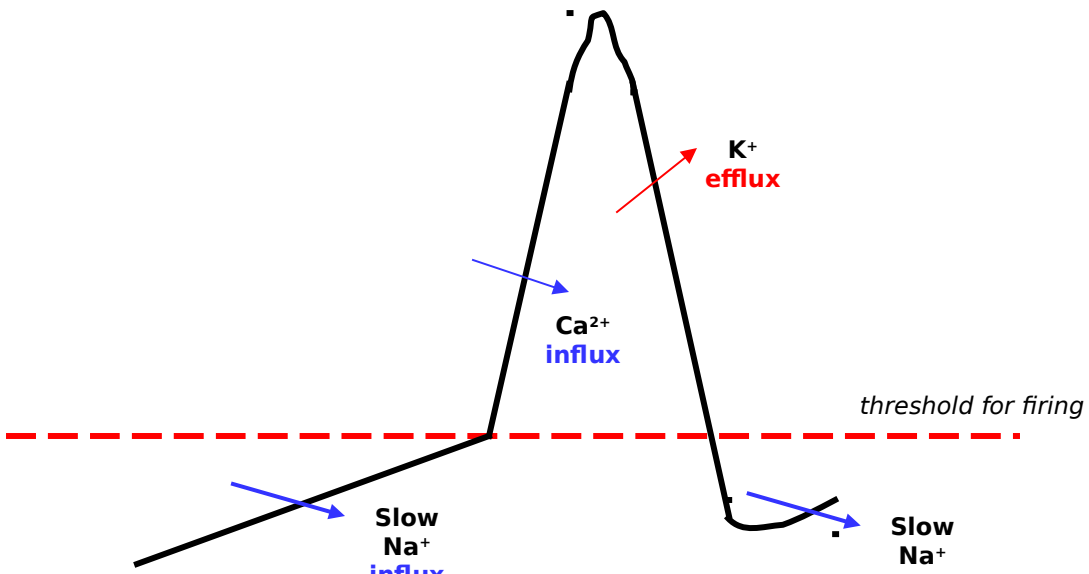
Purkinje Cell

Normal Cardiac Electrophysiology



Pacemaker Cell

Normal Cardiac Electrophysiology

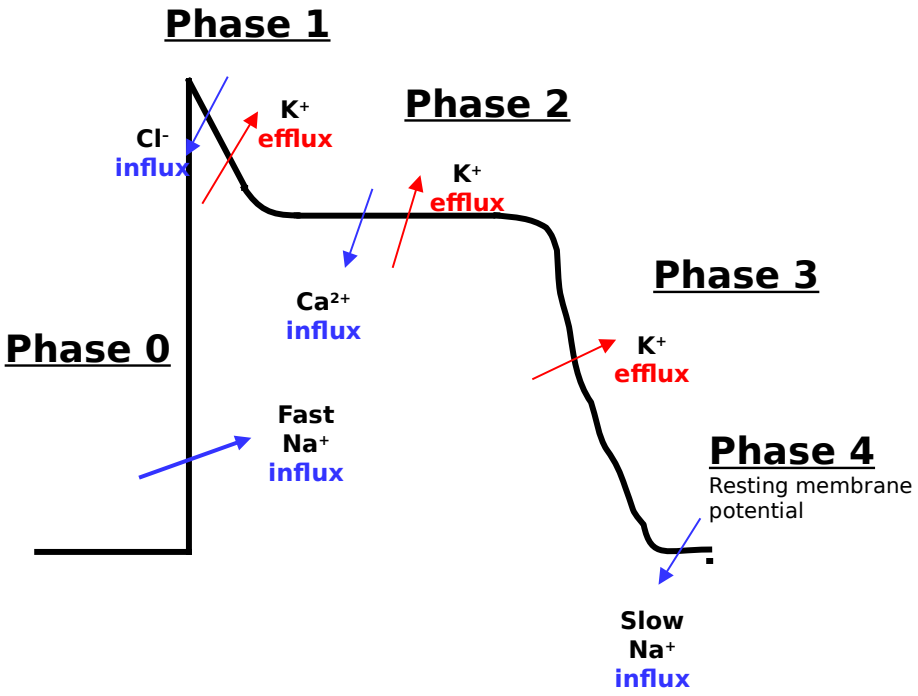


Pacemaker Current = I_f

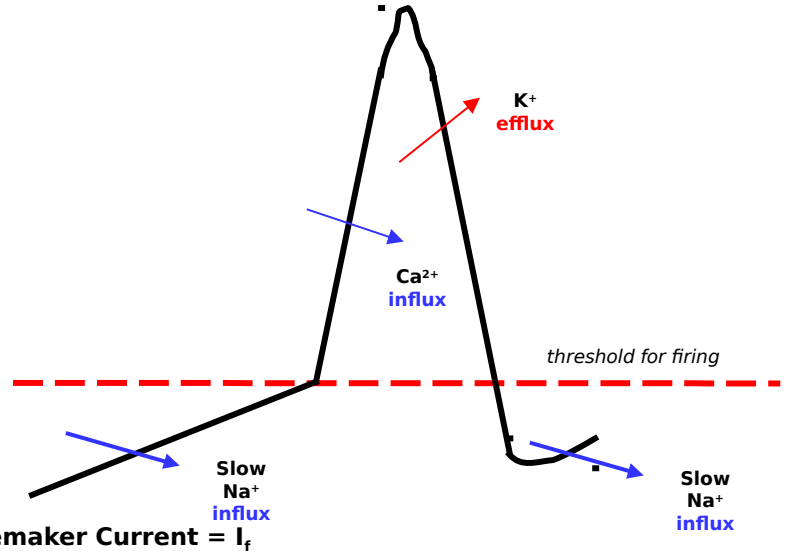
Spontaneous depolarization

Normal Cardiac Electrophysiology

Purkinje Cell



Pacemaker Cell



Pacemaker Current = I_f

Spontaneous depolarization

Cough

What **MEDICATIONS** are you on (if any)? → STOP any BETA blockers or ACE inhibitors (replace w/ other drugs)

Are you a SMOKER?
Any hints of pulmonary disease?
If so, do a CXR, bronchoscopy
If not, check other causes FIRST

How long has the cough been going on?

- 8 weeks or more? **CHRONIC**
- Less than 3-4 weeks? **ACUTE**
  - Resolves on it's own
  - Usually URI, flu, etc.
  - Treat symptoms

CHRONIC

#1 – Treat for **PND** (i.e., Sudafed, etc.)
85% are post-nasal drip (PND)

- Does not respond to PND therapy?
- Face feels full?

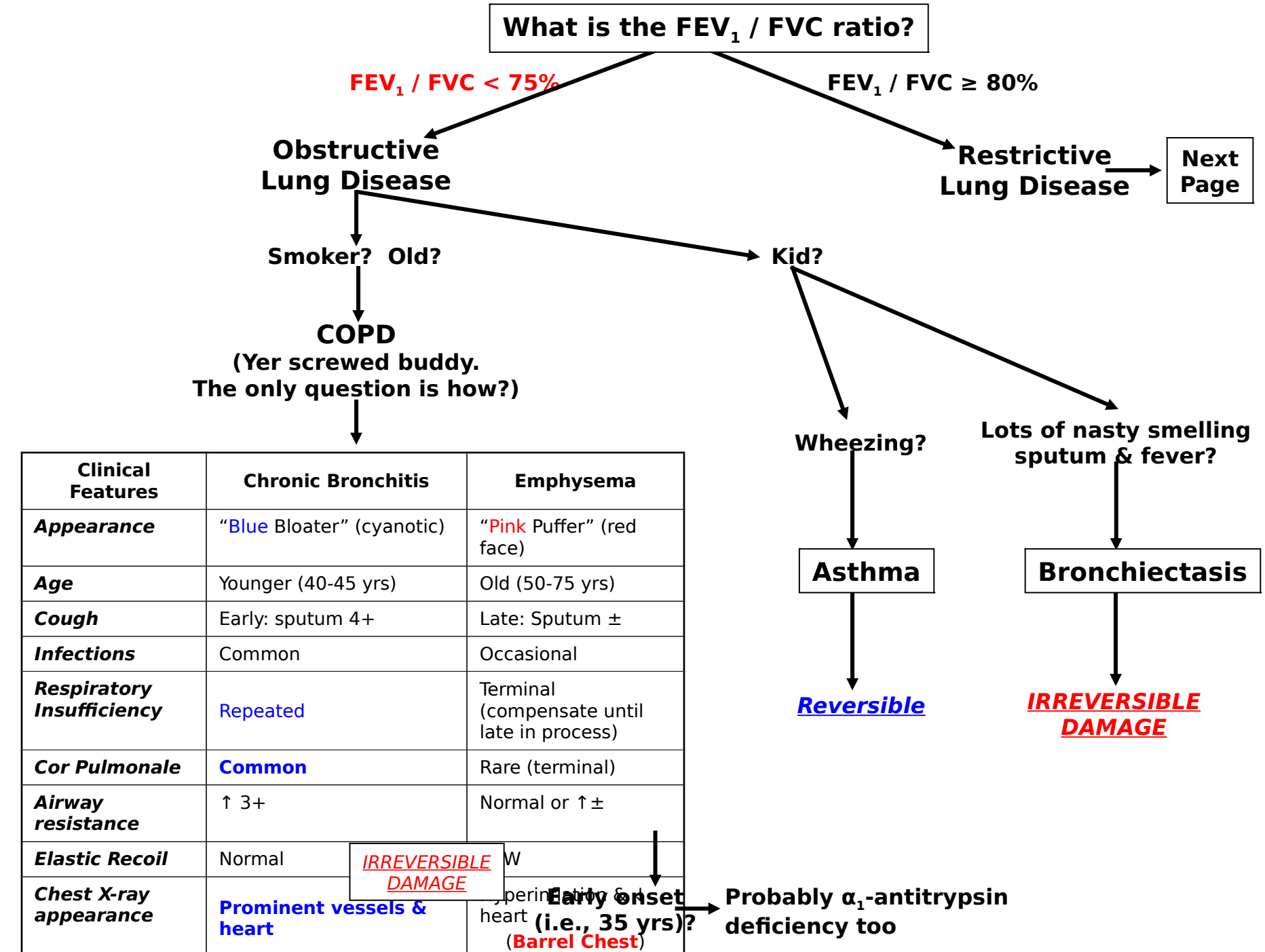
#2 – Treat for **ACUTE SINUSITIS**
X-ray sinuses

- Does not respond to therapies above?
- Dyspnea/cough after exercise or waking at night?

#3 – Test/treat for **ASTHMA**
Spirometry & methacholine challenge tests → No asthma? → #4 – Test/treat for **GERD**
History usually no help
Start over if this fails

Hemoptysis

- #1 – Make sure its really hemoptysis (red, frothy pink)
  - Hematemesis (from GI tract) → dark, like coffee grounds
  - Upper respiratory tract (nasal) or oral bleeding (i.e., dry winter air nosebleeds or gum bleeding)
  - Periodontal bleeding
- #2 – How MUCH blood are we talking about?
  - Massive = 50cc (~4-5 Tbsp) at once or over a few hours
    - Medical emergency requiring aggressive treatment
  - Minimal → usually smokers (chronic bronchitis) or infectious diseases
    - Treat as outpatient
- #3 – Radiograph (CXR) to find source of blood
  - Sometimes patients feel source of blood (‘something feels funny here)
- #4 - Bronchoscope



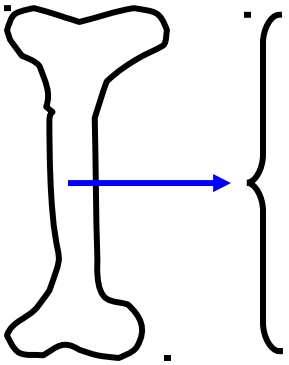
Clinical Features	Chronic Bronchitis	Emphysema
Appearance	"Blue Bloater" (cyanotic)	"Pink Puffer" (red face)
Age	Younger (40-45 yrs)	Old (50-75 yrs)
Cough	Early: sputum 4+	Late: Sputum ±
Infections	Common	Occasional
Respiratory Insufficiency	Repeated	Terminal (compensate until late in process)
Cor Pulmonale	**Common**	Rare (terminal)
Airway resistance	↑ 3+	Normal or ↑±
Elastic Recoil	Normal	↓
Chest X-ray appearance	**Prominent vessels & heart**	Hyperinflation & heart (**Barrel Chest**)

All characterized by:
- Reduced expansion of lung
- Reduction in total lung capacity
- Proportionate reduction in FEV_1 & FVC

Restrictive Airway Diseases

DISEASE	CAUSE(S)	RISK GROUP(S)	PATHOPHYSIOLOGY	CLINICAL FEATURES	HISTOLOGICAL FEATURES
Acute Respiratory Distress Syndrome (ARDS)	• Shock • Infection/sepsis • Trauma • Aspiration • O_2 toxicity	Adults Any age	• Initiated by damage to alveolar endothelium & Type II pneumocytes • Impaired gas exchange due to pulmonary hemorrhage, pulmonary edema, or atelectasis • Complement activation, sepsis	• Acute dyspnea, resp. failure • Hypoxia (cyanosis) • Heavy, wet lungs • Bilateral diffuse infiltrate (X-ray) • Honeycomb lung (end-stage)	• HYALINE membranes in alveoli • Diffuse alveolar damage
Sarcoidosis	Unknown	Females Young Black	• Interstitial fibrosis; diagnosis of exclusion (rule out infection, occupational sources of granulomas) • Requires biopsy demonstrating non-caseating granulomas (rule out TB)	• Dyspnea on exertion • Dry cough, fever, fatigue • Bilateral HILAR lymphadenopathy • Uveitis & parotitis (Mikulicz's) • Polyarthritis, dry eyes • Anergy to skin tests	• Interstitial pneumonitis • Non-caseating granulomatous lesions • Schaumann bodies • Asteroid bodies • Lungs & other organs
Hypersensitivity Pneumonitis (Farmer's Lung)	Exposure to ORGANIC antigens	Occupational risk (farms, birds, etc.)	• Type III & IV hypersensitivity rxn • Exposure to organic antigen • Chronic interstitial inflammation • Alveolar damage → fibrotic lung	• Can be acute or chronic • Dry cough • Chest tightness • General malaise, fever	• Interstitial pneumonitis • Many non-caseating granulomas • Fibrosis • Obliterative bronchiolitis
Idiopathic pulmonary fibrosis	Unknown	Males 50-60 yrs Smokers	• Chronic inflammation of alveolar wall, fibrosis, cystic spaces • Fatal within 3 years	• VELCRO-like rales, lower lobes • Honeycomb lung (end stage) • Finger-clubbing	• Usual interstitial pneumonitis • Fibrosis of alveolar wall

B Cell Lymphoblasts & Lymphomas



L0 stem cell

↓

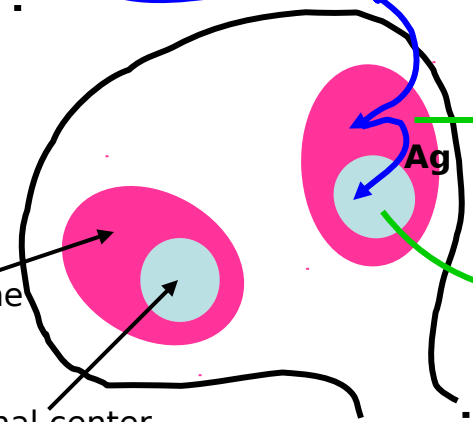
Lymphoblast (tdt+, CD10/CALLA, CD19, ~~CD20~~) → ALL

↓

Naïve B cell (CD5+, CD23+) → CLL & SLL

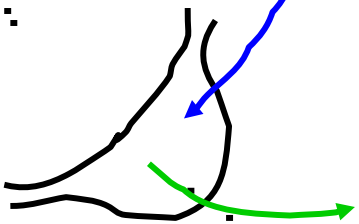
CD5+ CD23+

GI Tract



Mantle zone lymphoma

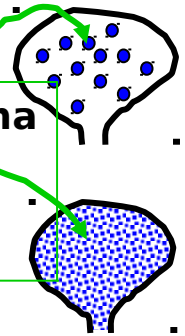
- Follicular lymphoma
- DLB & CL
- Hodgkin disease
- Burkitt lymphoma



Helicobacter pylori infection

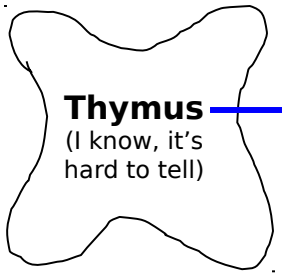
↓

MALTomas
(***marginal*** zone lymphoblasts)



**Know these two pictures in the glass slides

T Cell Lymphoblasts & Lymphomas



T cell Lymphoblast (CD4+, CD8+)
[uncommitted]

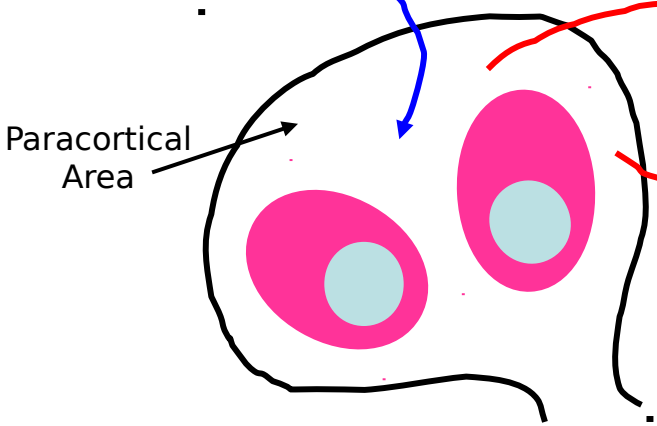
Committed T cell (CD4+ or CD8+)

T cell lymphoblastic leukemia or lymphoma

ALL (T cell)

Mediastinal Mass

Peripheral T cell lymphoma
- Cutaneous T cell lymphoma



HTLV-1 Infection

Adult T cell lymphoma/leukemia

CLINICAL DIFFERENCES BETWEEN HODGKIN AND NON-HODGKIN

Robbins Table 15-8

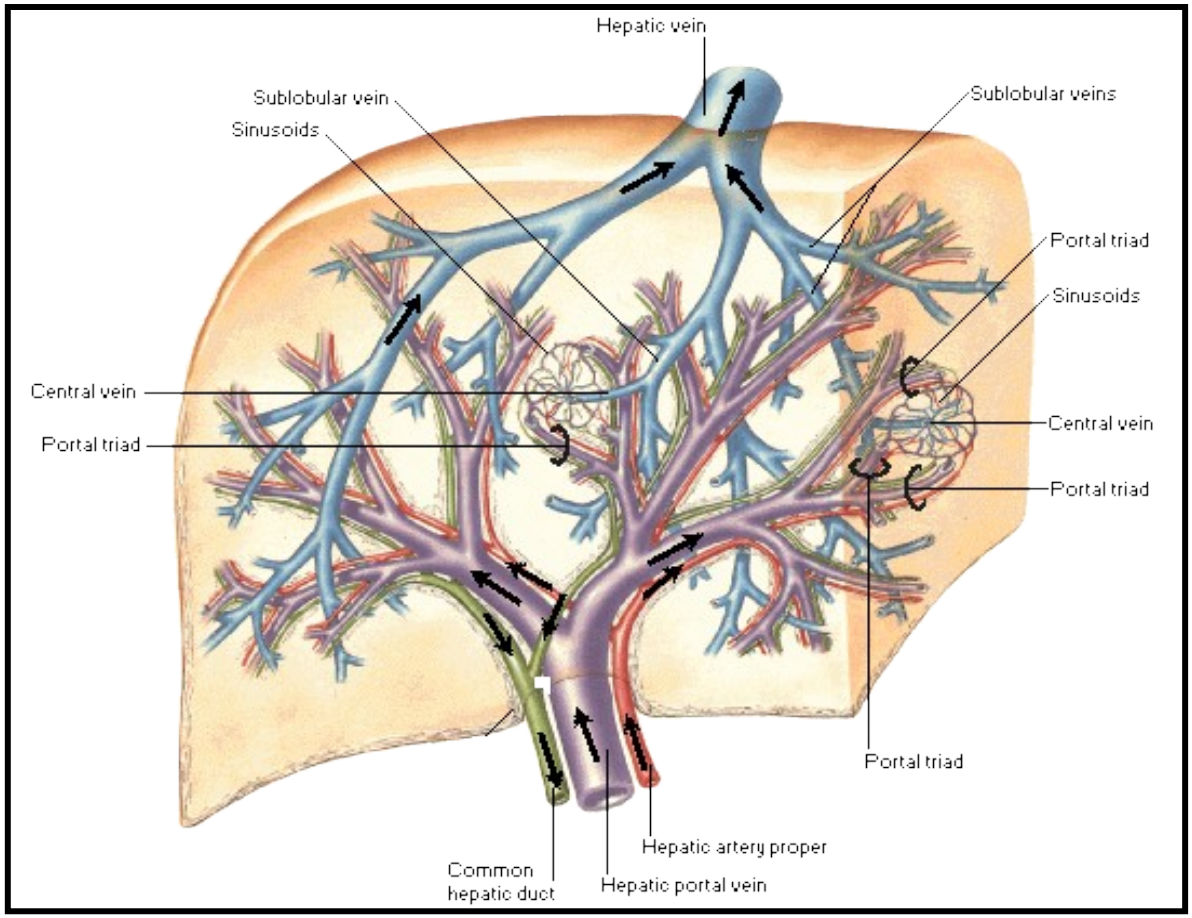
Hodgkin Disease	Non-Hodgkin Lymphoma
• More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic) • Orderly spread by contiguity • Mesenteric nodes and Waldeyer ring rarely involved • Extranodal involvement uncommon	• More frequent involvement of multiple peripheral nodes • Noncontiguous spread • Waldeyer ring and mesenteric nodes commonly involved • Extranodal involvement common

Vascular & Duct Systems

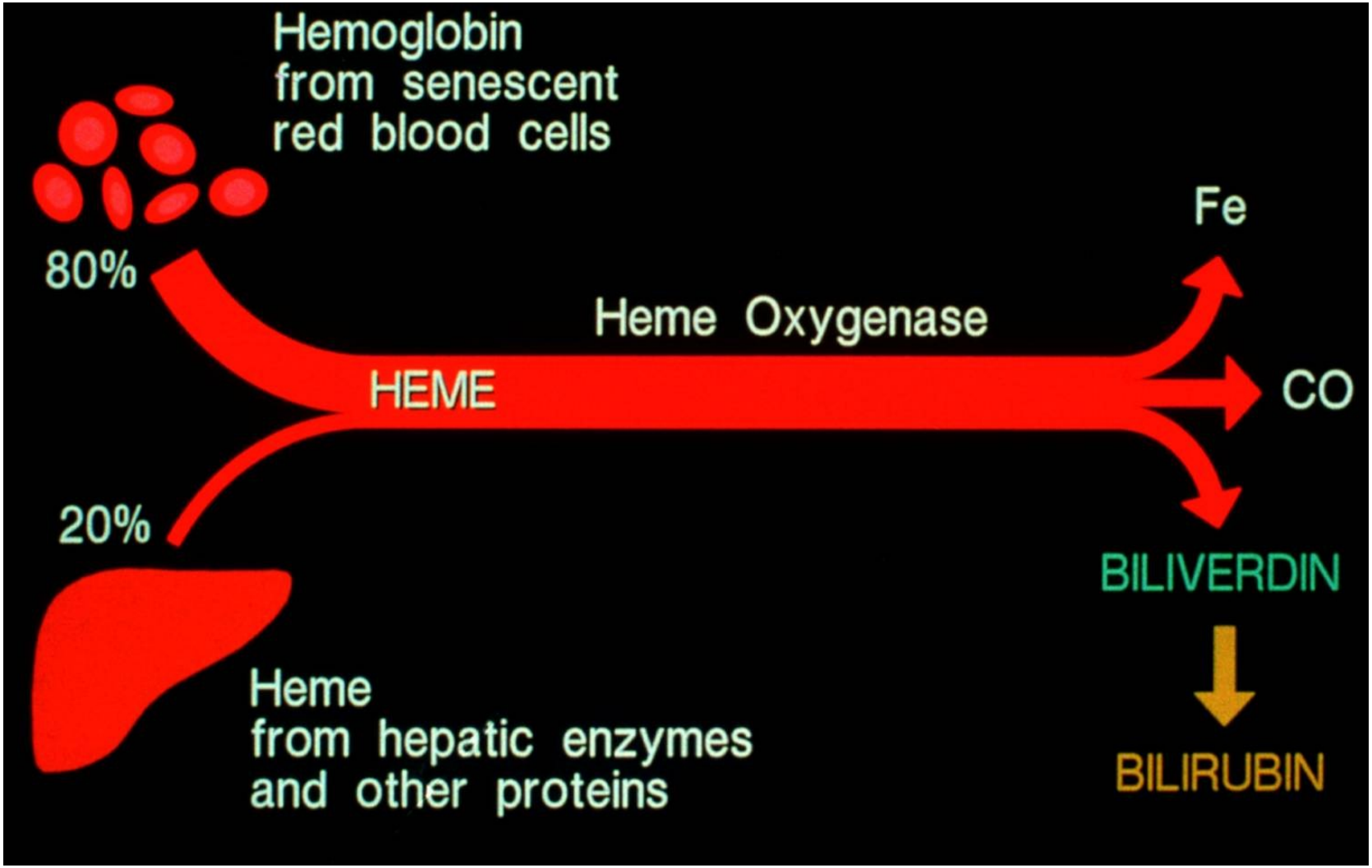
Intrahepatic

What does the liver do?

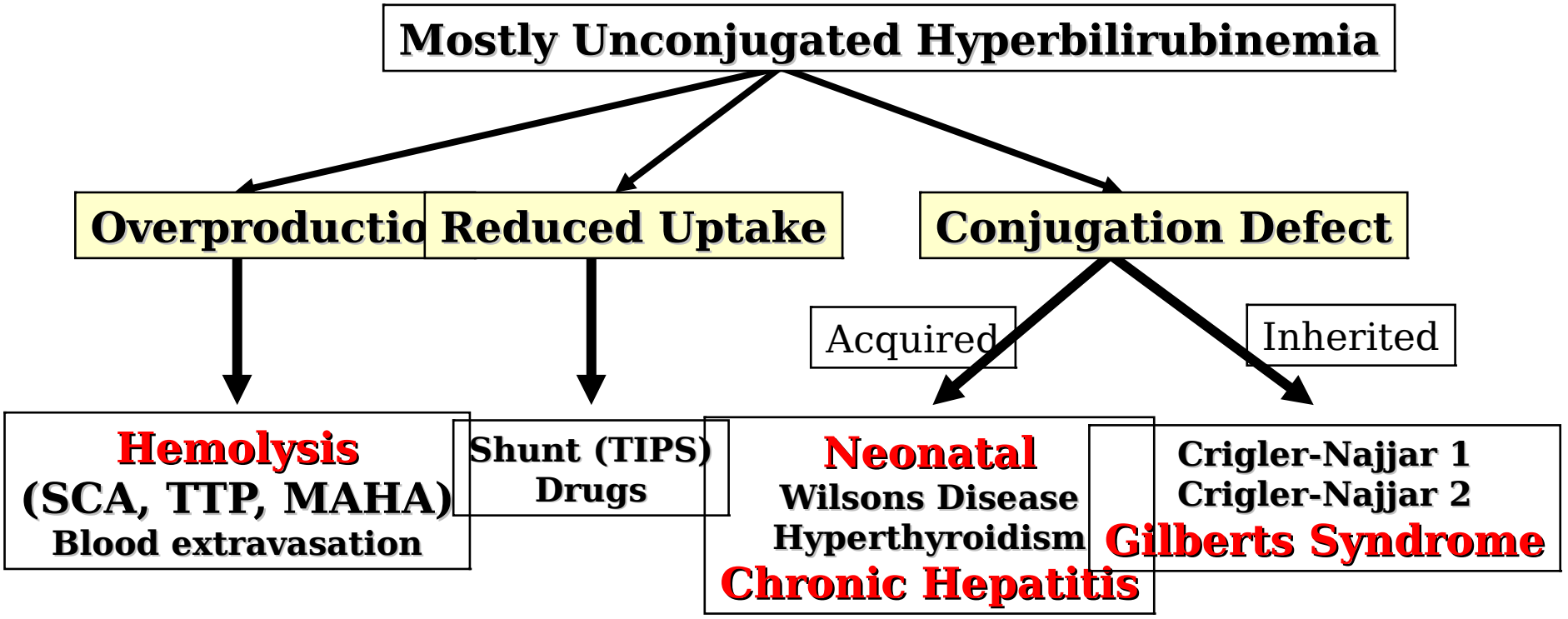
- **Participates in glucose homeostasis**
  - **Gluconeogenesis ←→ Glycolysis**
- **Synthesizes critical proteins**
  - **Albumin, clotting factors, globulins**
  - **Amino Acid transformation**
- **Serves as immune organ**
  - **Filters intestinal bacteria**
- **Synthesizes lipoproteins**
- Excretes/biotransforms
  - Bilirubin, toxins
- **Stores vitamins & minerals**



Sources of Bilirubin



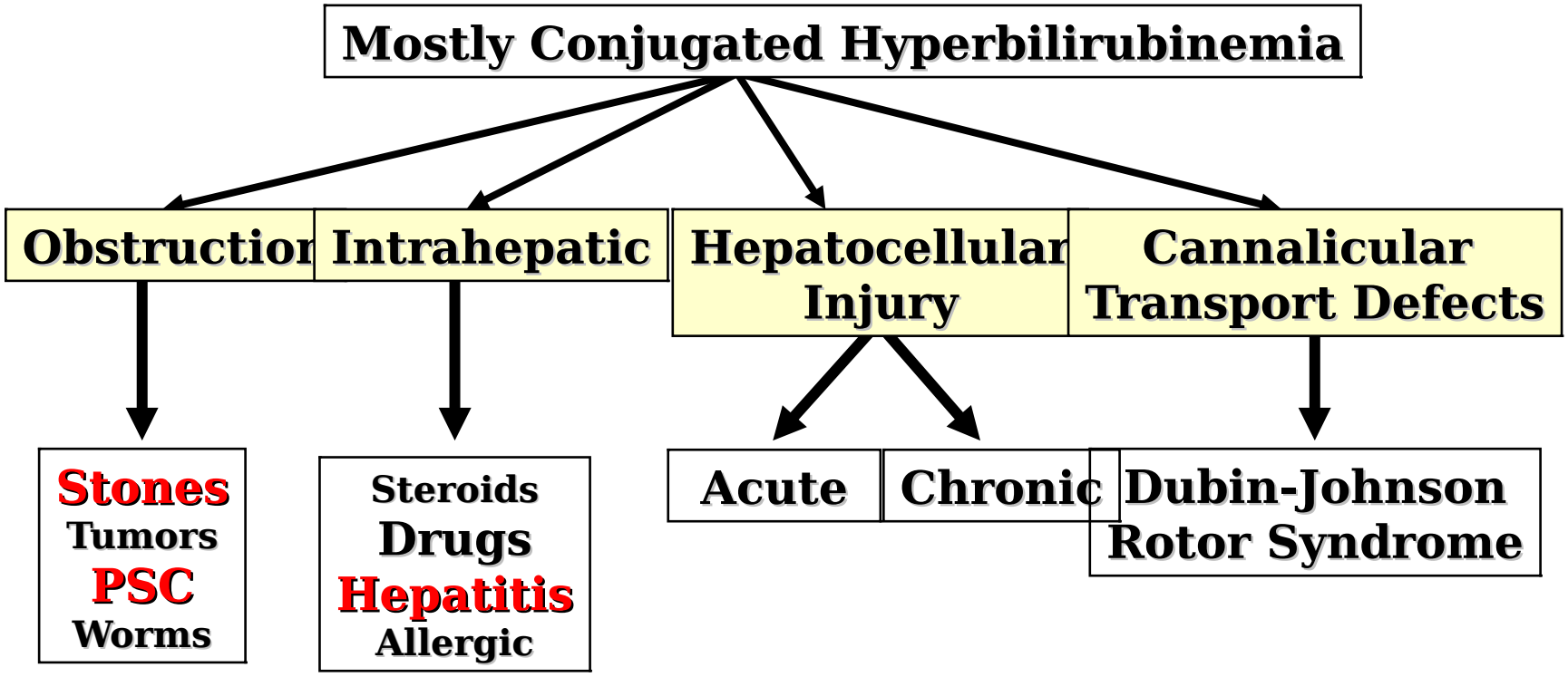
Indirect Bilirubin Elevation



Isolated Bilirubin Elevation

- Clinical presentation – Gilbert Syndrome:
  - Young adult (male or female)
  - Feels fine (often an incidental lab discovery)
  - Total bilirubin (T bili) ↑ slightly (only to ~2.5)
  - Usually follows some sort of stress (i.e., infection)
- Clinical presentation – Crigler-Najjar
  - Type 1 = Jaundiced infant
  - Type 2 = Fatal
- Gilbert Syndrome or Crigler-Najjar
  - Elevated Bilirubin without anemia
  - Check record for history of LAE elevations
- Fractionate bilirubin
  - Should all be indirect/unconjugated
  - Reticulocytes, smear, CBC should be normal
  - Increased bilirubin level with stress, fasting
  - Should be no bilirubin in the urine or any other LAE abnormality

Direct Bilirubin Elevation



LIVER DISEASES

JAUNDICE

- Deposition of bilirubin in CT (elastic fibers)
- Clinical signs of liver damage:
1. Clay-colored stools
2. Dark urine
3. Jaundice

UNCONJUGATED HYPERBILIRUBINEMIA

NEWBORN JAUNDICE

- Increased bilirubin production
- Decreased synthesis of glucuronyl transferase

GILBERT'S SYNDROME

- Common, 5% pop.
- AD, asymptomatic
- Reduced gucuronyl transferase (UGT) activity
- Decreased bilirubin uptake by liver

CRIGLER-NAJJAR SYNDROME

- Type 1: AR, fatal, totally lacking UGT enzyme
- Type 2: AD, nonfatal, UGT partially functional

CONJUGATED HYPERBILIRUBINEMIA

DUBIN-JOHNSON SYNDROME

- AR, asymptomatic
- Defected transport into bile duct
- Very dark pigment discolors liver

ROTOR SYNDROME

- AR
- Similar Dubin-Johnson
- No liver pigmentation

VASCULAR

PORTAL HYPERTENSION

- Due to portal venous obstruction
- Pre-hepatic: portal and splenic vein obstruction by thrombosis
- Intra-hepatic: intra-hepatic vascular obstruction by cirrhosis, metastatic tumor, schistosomiasis
- Post-hepatic: venous congestion due to constrictive pericarditis, CHF, Budd-Chiari syndrome, etc.
- Venous collaterals develop in submucosal veins of esophagus and stomach, internal hemorrhoidal veins, and superficial abdominal veins
- Ascites due to increased venous and lymphatic pressure, and to decreased plasma oncotic pressure from decreased albumin production

BUDD-CHIARI SYNDROME

- Thrombotic occlusion of major hepatic veins
- Associated w/ polycythemia vera, hepatocellular carcinoma
- Complication of preg
- Causes portal HTN
- Hepatomegaly, weight gain, ascites, abdominal pain, profound centrilobular congestion and necrosis

INFARCTION

- Uncommon, due to dual blood supply

HEPATIC ENCEPHALOPATHY

- Severe loss of hepatic fxn
- Shunting of blood around liver
- Toxic metabolites accumulate in blood; ammonemia
- Ammonia toxic to brain

CONGESTIVE HEART FAILURE

- Chronic right-sided HF
- Nutmeg liver: dark red congested centrilobular areas alternating w/ pale portal areas
- Cardiac sclerosis of liver is centrilobular fibrosis

HEPATORENAL SYNDROME

- Renal failure in presence of liver failure w/o intrinsic renal problems
- Decreased renal perfusion pressure

BILIARY TRACT OBSTRUCTION

- Etiology: gallstones or tumors in adults; biliary atresia in children
- Sx: jaundice, dark urine, light stools; biliary colic w/ distention of bile duct; pruritis due to accumulation of bile acids in blood
- Acute cholangitis: fever, RUQ tenderness due to ascending bacterial infection (normal flora)
- ↑ conjugated bilirubin
- ↑ AP, GGT
- ↑ AST, ALT < 10x
- Dx: ultrasound shows dilated bile duct
- Histo: inflammation in portal areas; bile duct proliferation; hepatocyte feathery degeneration; portal fibrosis; cirrhosis

ACUTE LIVER DISEASES

- Disordered excretion of bilirubin
- Hemolysis: ↑ unconjugated bilirubin, nl ALT, nl AST, ↑ LDH (RBCs)
- If rule out hemolysis, then must be biliary tract obstruction or acute

ACUTE HEPATITIS

- ↑ conjugated bilirubin → dark urine
- ↑ AST, ALT, ↑ LDH
- ↑ AP, GGT minimally
- Most are asymptomatic
- Ballooning degeneration of hepatocytes
- Cytotoxic T cell infiltrates kill hepatocytes

HEPATITIS A

- Contaminated H_2O, seafood
- Fecal-oral tx
- NO chronic disease
- Anti-HAV IgM indicates active infection

HEPATITIS B

- Sexual, parenteral, mom → baby = chronic
- Chronic carrier state or chronic hepatitis
- ↑ risk hepatocellular cancer
- HBsAg: marker of HBV DNA; before jaundice
- anti-HBc: first immune response; covers window
- HBeAg: marker of infectious Dane particles
- anti-HBs, anti-HBe clear infection

HEPATITIS C

- Serum, blood transfusion
- HI RATE of chronic hepatitis
- Anti-HCV Ab diagnostic
- ↑ risk hepatocellular cancer

HEPATITIS D

- Co-infection w/ HBV
- Replication requires HBsAg coating

HEPATITIS E

- Fecal-oral
- Pregnant ♀ 20% mortality
- Developing countries

ALCOHOLIC HEPATITIS

- Triad: neutrophil large fat vacuole Mallory bodies
- AST, ALT < 10x
- AST > ALT

TOXIC HEPATITIS

- Acetaminophen + alcohol = bad
- Metabolite is tox
- AST, ALT > 100x
- ↑ PTT (marked)
- ↑ LDH 10-40x

ISCHEMIC HEPATITIS

- ↓ blood flow (sho
- cells near centra damaged first
- AST, ALT > 100x
- ↑ PTT (marked)
- ↑ LDH 10-40x

CHRONIC LIVER DISEASES

CHRONIC HEPATITIS

• Evidence of hepatitis for > 6 months following acute disorder
• Etiology: viral (HCV 10x HBV) and alcoholic hepatitis; NASH (obese and diabetics); hemochromatosis; Wilson's Disease, inborn errors of metabolism (α1-antitrypsin deficiency, galactosemia, glycogen storage diseases)
• Sx: many asymptomatic w/ ↑ ALT; weight loss, fatigue, anorexia; jaundice rare
•Lab: persistent ↑ AST, ALT < 10x; ALT more sensitive and specific than AST
• Grade: severity of inflammation
• Stage: extent of fibrosis
• Prognosis: depends on both grade and stage; progression to cirrhosis: male, over 40 y/o, alcohol, HIV+
•Tx: steroids delay or prevent cirrhosis; IFN can induce remission in HBV/HCV patients; combined IFN/ribavirin can induce complete remission in HCV

CIRRHOSIS

• End-stage of scar formation and distorted regeneration of hepatocytes
• Etiology: usually ethanol or HCV; also chronic bile duct obstruction and congenital metabolic errors
• Portal HTN develops late, and may be first indication of disease
• Morph: nml liver progresses to chronic active hepatitis w/ bridging fibrosis (collagen bands extending from portal areas)
• Hallmark of cirrhosis: nodules of hepatocytes devoid of central veins and enclosed by bands of fibrous tissue; micronodular (< 3mm): alcoholic cirrhosis; macronodular (> 3mm): viral hepatitis
• Lab: non-diagnostic; ↑ ALT, AST > ALT; ↑ PT, ↓albumin; ↑ Ig
• Prognosis: in severe portal HTN, death occurs via bleeding esophageal varices, hepatic encephalopathy, or infection

PRIMARY BILIARY CIRRHOSIS

• **Middle-aged women**
• Chronic, progressive autoimmune cholestatic liver disease
• Destruction of intrahepatic bile ducts, portal inflammation & scarring, cirrhosis, liver failure
• Insidious onset: pruritis, hepatomegaly; jaundice, xanthomas
• Lab: ↑ AP, ↑ cholesterol, **↑ AMA**, ↑ ceruloplasmin
• Assoc. w/ Sjogren's, scleroderma, thyroiditis, Raynaud's, membranous glomerulonephritis, celiac disease

PRIMARY SCLEROSING CHOLANGITIS

• **Middle-aged men**
• Chronic progressive cholestatic liver disease
• Inflammation, obliterative fibrosis, segmental dilation of intra- & extra-hepatic bile ducts
• **Assoc. w/ ulcerative colitis**
• **↓ AMA**
• Beading on ERCP
• Leads to cirrhosis, liver failure

INBORN ERRORS OF METABOLISM

• Accumulations in hepatocytes lead to cirrhosis

HEMOCHROMATOSIS

• **Young MEN** (20's-30's)
• AR, chromosome 6, HLA gene
• Unregulated intestinal absorption of iron
• Iron accumulates in parenchymal tissues & synovial joints as ferritin & hemosiderin in liver & other organs
• Hepatomegaly, abdominal pain, skin pigment, diabetes, arthritis, cardiac dysfxn, **hypogonadism**
• Tx: **phlebotomy**

WILSON DISEASE

• **Young MEN**
• AR, chromosome 13
• Defective secretion of copper into bile for elimination
• Copper accumulates to toxic levels in liver, brain, eyes
• Hepatitis w/ Mallory bodies, fatty change, Cu accumulation
• Lab: **↓ ceruloplamin**
• **Keyser-Fleischer rings in eye**
• Tx: chelating agents

α-1-ANTITRYPSIN DISEASE

• AR, chromosome 14
• Serum protease inhibitor made in liver
• Glu-Lys substitution prevents proper protein folding; can't be secreted, accumulates in hepatocytes
• Lung damage due to lack of enzyme
• Sx: neonatal hepatitis, or cirrhosis in a child or an adult
• Comp: lung & hepatocellular cancer
• Tx: liver transplant, don't smoke

NEOPLASMS

MALIGNANT

METASTASES

• Overwhelming majority of liver cancers

HEPATOCELLULAR CARCINOMA

• Males, mid- to late decades
• Assoc. w/ chronic HCV/HBV infections, alcohol leading to cirrhosis; also hemochromatosis, tyrosinemia
• Aflatoxin from aspergillus
•HBV/aflatoxin synergistic
• Massive hepatomegaly
• Unifocal mass or multifocal nodules, or diffusely infiltrative
• Pink-yellow in color
• RUQ pain, wt loss, ↑AFP
• Prog: death w/in 6 mos.

HEPATIC ANGIOSARCOMA

• PVC workers
• Thorotrast (contrast mat'l no longer used)

CHOLANGIOCARCINOMA

• Arises from intrahepatic biliary tree
• ↑ Risk: thorotrast, *Clonorchis sinensis*, Caroli disease
• Unifocal mass or multifocal nodules, or diffusely infiltrative
• Typically pale in color
• Rarely resectable

BENIGN

HEPATIC ADENOMA

• Associated w/ oral contraceptive use

HEMANGIOMA

• Incidental finding; surgery; no consec

Liver Chemistry Panel

- ***Evaluate injury to hepatocytes & bile ducts***
  - ALT, AST, Alk Phos
- ***Evaluate liver's biosynthetic capacity***
  - Albumin, Prothrombin time, lipoproteins
- ***Evaluate transport of organic anions***
  - Bilirubin
- ***Evaluate altered immunoregulation or virus***
  - ANA, AMA, ASMA, SPEP, HAV, HBV, HCV…
- ***Evaluate hypersplenism***
  - Platelet count (indirect)

- ***Markers of <u>Hepatocellular</u> Injury***
  - ALT (SGPT)
  - AST (SGOT)
- ***Markers of <u>Cholestasis</u> (extrahepatic biliary obstruction)***
  - ↑ Alkaline Phosphatase
  - ↑ Bilirubin (conjugated/direct)
  - GGT

<u>Normal Values</u>:

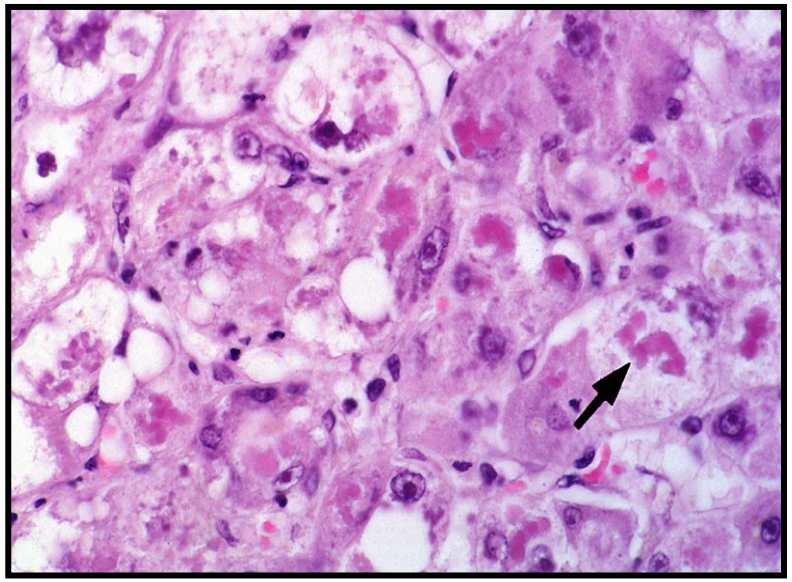
- AST = 5 – 40 U/L
- ALT = 5 – 40 U/L
- Alkaline phosphate = 50 – 120 U
- Total bilirubin = 0.5 – 1.0 mg
- Direct bilirubin = 0.5 – 0.9 mg

<u>Key/Classic Findings</u>:

- ↑↑ Alk Phos + ↑ direct bili + normal/mild ↑ ALT & AST → Biliary tract disease/obstruction (e.g., gallsto
- ↑↑↑↑ AST & ALT (i.e., 10X normal…in the 1,000's) → widespread hepatic destruction
- ↑ AST & ALT to ~ 2-3X normal, with AST > ALT → alcoholic cirrhosis
- Small, incidental ↑ total bili (i.e., ~2.5) + stress + clinically normal young patient → Gilbert Syndrome
- Middle-aged woman w/gradual onset pruritis & scleral icterus + ↑anti-mitochondrial antibody (AMA) →
- Young man w/ signs of liver damage + inflammatory bowel disease (ulcerative cholitis) + NO ↑ AMA → P
- ↑ indirect (unconjugated) bilirubin → intravascular hemolysis (i.e., sickle cell disease)

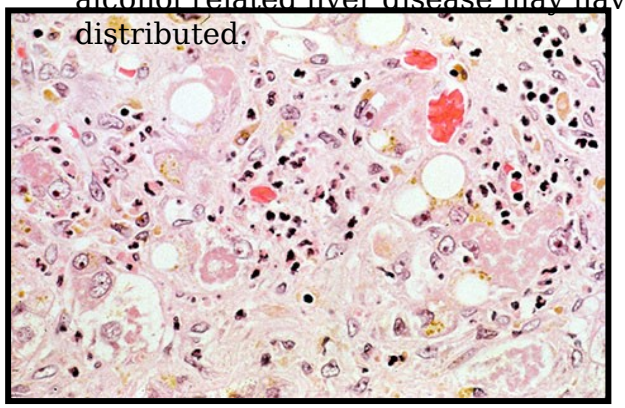
Acute alcoholic hepatitis

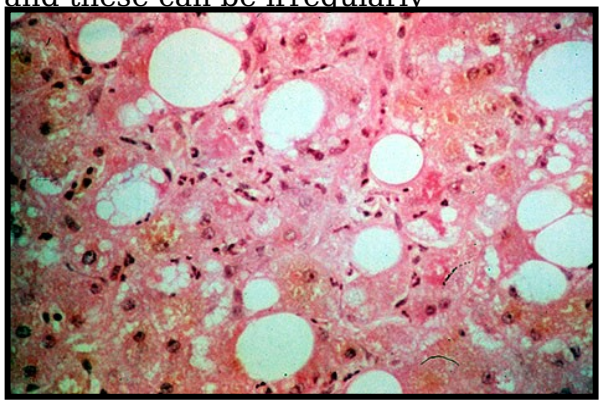
- **Liver cells show macrovesicular & microvesicular fatty change**
- **Alcoholic hyaline (Mallory) bodies made up of aggregates of intermediate cytokeratin filaments**
- **Individual necrosis (“dropout”) of hepatocytes (acidophilic bodies)**
- **Scattered neutrophils**



Mallory bodies (aka. alcoholic hyaline) are highly variable in appearance. The stain color may vary from magenta to bright red; it is usually slightly more hematoxyphilic than surrounding cytoplasm. A perinuclear location is common; ring forms may occur. The irregular clumps of hyalin have been likened to the rough irregular coils of rope.

Mallory bodies appear as irregular condensations of proteinaceous material within the cytoplasm of hepatocytes, commonly in cells that are undergoing ballooning degeneration. This phenomenon helps in the recognition of Mallory bodies. Scanning the slide at 10x, searching for large pale cells with dark condensations in the midst of a wispy cytoplasm often yields a quick reward; the nature of the cytoplasmic material is readily confirmed at high power (40x). If one begins the search at high power, there is a great chance that one will be "lost in the forest for the trees". The ordinary case of alcohol related liver disease may have only several affected cells, and these can be irregularly distributed.





Renal Failure

Azotemia
Oliguria/Anuria

Azotemia = ↑ BUN & creatinine due to ↓ GF
Anemia → practically all patients present wit
Why? They're no longer making erythropoiet

How does the patient present?

Where's the problem?

Pre-renal
Problem:
The BODY

Renal
Problem:
The BEAN

Post-renal
Problem:
The BLADDER

What's the cause?

Cause: Hypovolemia
- **Sepsis**
- **Shock**
- **Heart failure**

(no flow TO the bean)

NephrItic Syndrome
- **Azotemia**
- **Hematuria**
- **Red cell casts**
- **Hypertension**
- **Mild edema**
- **Mild proteinuria**

- **Membranoproliferative glomerulonephritis**
- **Post-infection GN (post-strep)**
- **Rapidly progressive GN (crescentic)**
- **IgA nephropathy (Berger disease)**
- **Alport syndrome**

NephrOtic Syndrome
- **MASSIVE proteinuria**
- **SEVERE edema**
- **Hyperlipidemia**
- **Hypercholesterolemia**
- **NO hematuria, azotemia, or HTN at outset**

- **Minimal change disease**
- **Membranous glomerulonephritis**
- **Focal segmental glonerulosclerosis**
- **Diabetic nephropathy**
- **SLE nephropathy (nephritic or nephrotic)**
- **Renal amyloidosis**

Cause: Obstruction
- **Old dude with BPH**
- **Cancer**
- **Stones**

(no flow OUT the bean)

LABS:

BUN > 20
Urine is concentrated
Urine [Na^+] low (< 10 mEq/L)
↓ fractional excretion of Na^+

BUN < 20
Urine is dilute
Urine [Na+] high (> 20 mEq/L)
↑ fractional excretion of Na^+
↓ CO_2
Cells/casts → tubular injury

Ultrasound

May present as polyuria
(w/ high urine [Na+] & unconcentrated urine)

Problems with the B

See Harrison's pg. 1581 Fig. 274-1

How does the patient present?

Painless Hematuria

Where's the problem?

Pre-renal
Problem:
The BODY

Renal
Problem:
The BEAN

Post-renal
Problem:
The BLADDER

What's the cause?

Cause: Hypovolemia
- **Sepsis**
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(no flow TO the bean)

NephrItic Syndrome

NephrOtic Syndrome

Cause: Obstruction
- **Old dude with BPH**
- **Cancer**
- **Stones**

(no flow OUT the bean)

LABS:

BUN > 20
↑ fractional excretion of Na^+

↑ fractional excretion of Na^+
↓ CO_2

Ultrasound

For systemic diseases, get an ANA te

Urinary bladder → GROSS hematuria
(guys don't mess around here, they run screaming to emergency room)

Pheo's → NO hematuria
Younger
BP goes up & down

RENAL DISEASE

CONGENITAL

NUMBER

RENAL AGENESIS

BILATERAL

- Oligohydramnios
- Incompatible w/ life
- Potter's facies
- Large abdominal mass → pulmonary hypoplasia (lungs don't develop)

UNILATERAL

- More common
- Asymptomatic

POSITION

HORSESHOE KIDNEY

- Fused pelvic kidney
- May cause urinary tract obstruction

ECTOPIC

- Usually pelvis

COLLECTING SYSTEM

URETERAL DUPLICATION

- Most common anomaly of ureters
- May fuse together
- Entire collecting system may be duplicated

PARENCHYMA

AD POLYCYSTIC KIDNEY (ADPKD)

- ADULTS (age 15-30), AI
- Always bilateral
- Large kidneys w/ round cysts
- Berry aneurysm (circle of Willis → EARLY STROKE)
- Cysts on liver & other organs
- HTN, renal failure, hematuria, palpable mass(es)

AR POLYCYSTIC KIDNEY (ARPKD)

- Rare AR, NEONATES
- Palpable masses
- Large kidneys w/ radial cysts (sunburst)
- Hepatic fibrosis → portal HTN

ACQUIRED CYSTIC DISEASE

- Long-term DIALYSIS therapy
- ↑ risk of RCC

Abbreviations:
HTN = Hypertension
RCC = Renal cell carcinoma
RAA = Renin-angiotensin-aldosterone
IF = Immunofluorescence
EM = Electron microscopy

TUMORS

RENAL CELL CARCINOMA

- Most common ren
neoplasm
- OLD MEN aged 5
- ↑ risk for SMOKE
- Triad: **hematuria palpable mass, dull flank pain**
- Paraneoplastic sy
e.g., hyperparathyr
- 2° polycythemia (erythrocytosis) fro
erythropoietin
- HTN from ↑ renin
- 3 variants:
o Clear cell → chr. 3 deletion, VHL gen **most common**
o Papillary → trison MET oncogene
o Chromophobe → good prognosis
- Tx: resection
- Prog: 40% 5-yr su

WILMS' TUMOR

- KIDS (aged 2-4)
- Palpable flank ma
- Deletion of WT-1 suppressor gene on chromosome 11

TRANSITIONAL CELL CARCINOMA

- OLD MEN
- Painless hematuri
- Anywhere in urina collecting system
- Causes:
o β-naphthalamine (industrial exposu
o Smoking
o Analgesic abuse

NEPHROTIC SYNDROME

MINIMAL CHANGE DISEASE

- Most common cause of nephrotic syndrome in KIDS
- LM → NO change
- EM → **Fusion of foot processes**
- IF → Negative
- Lipid accumulation in renal tubular cells
- **Treat w/ steroids**

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

- MAC activates glomerular epithelial cells
- Adults → AIDS & IV drug users
- Recurs after transplant
- Hyalinosis – deposition of hyaline in GBM
- Does NOT respond to steroid tx

MEMBRANOUS GLOMERULOPATHY

- Most common cause of nephrotic syndrome in ADULTS
- LM/EM → **SPIKE & DOME** pattern seen with silver stains
- IF → **GRANULAR pattern**
- GBM thickened & wire loops due to immune complex deposition
- Does NOT respond to steroid tx

DIABETIC GLOMERULOSCLEROSIS

- Glycosylaton of GBM
- GBM markedly thickened
- **Kimmelstiel-Wilson nodules** seen w/ PAS & silver stains
- **Renal papillary necrosis**

AMYLOID KIDNEY

- **Congo red** - special stain that identifies amyloid deposits w/ **apple-green birefringence**

NEPHRITIC SYNDROME

RAPIDLY PROGRESSIVE GLOMERULOSCLEROSIS

- NOT a disease; assoc. w/ SLE (♀), anti-GBM disease (♂) & Goodpasture (kidney + lung)
- Dx: **renal biopsy → crescents**

POST-INFECTION GLOMERULOSCLEROSIS

- IF → **LINEAR pattern** of IgG dep
- Neutrophils infiltrate glome which are large & hypercellul
- IF → **lumpy-bumpy depos** of C3, IgG
- EM → humps on epithelial s of GBM

OTHERS

MEMBRANO-PROLIFERATIVE DISORDERS

- Kids or adolescents w/ nephrotic syndrome
- Type II (dense deposit dise often recurs after transplant
- Type I – tram track appear
- Type II – deposits of C3 & dense deposits

IgA NEPHROPATHY (Berger Disease)

- Young adults
- Sx: hematuria starts after inf recurs every few months
- Assoc. w. celiac (gluten sens. liver disease
- IF → MESANGIAL IgA depos
- 50% → end-stage renal failur
- Part of Henoch-Schonlein pur

RENAL

INTERSTITIAL NEPHRITIS

• Group of disorders w/ inflammatory infiltrates in interstitium (surrounding tubules)

DRUG-INDUCED NEPHRITIS

• Penicillin-derivatives, lomps diuretics, & NSAIDs
• Immune mediated
• Reversible (stop drug)

ACUTE PYELONEPHRITIS

• Most often ascending infection by *E. coli*
• Hematogenous spread from infected cardiac valve (staph), TB dissemination, aspergillus
• Costovertebral tenderness
• Very sick – fever, chills, flank pain, polyuria, burns
• **WBC (neutrophil) casts in urine (pathognomonic)**

HYDRONEPHROSIS

• Dilatation of renal pelvis & collecting system
• Papillae flattened & cortex atrophied

OBSTRUCTIVE UROPATHY

• Renal parenchyma; tubule blocked by tumor necrosis, BJ proteins, uric acid, etc.
• Renal pelvis and ureters:
•*Urolithiasis*: diet and fluid intake; very painful
• Calcium stones: most common; hypercalcemia due to hyperparathyroidism or malignancy of bone; ↑ intestinal uptake or ↓ tubular absorption
• Uric acid stones
• Magnesium ammonium phospate (infection) stones: urease-splitting bacteria *(H. pylori, P. vulgaris, Staph);* staghorn calculi
• *Papillary necrosis*: analgesic abuse (phenacetin (Europe), NSAIDs) and diabetes
• *Neoplasm*:: transitional cell carcinoma in calyx
• Ureters: pelvic tumor, fibrosis, abscess, hematoma, pregnancy, endometriosis
• Bladder and urethra: prostatic hyperplasia

ACUTE RENAL FAILURE

• Rapid deterioration in renal function w/ azotemia
• **Prerenal**: ↓ blood flow to the kidneys
o BUN > 20
o Hypovolemia (sepsis, shock, heart failure, dehydration, bleeding, etc.) → oliguria w/ LO urine [Na+]
• **Renal**: MOST COMMON
o Nephritic syndromes (see previous)
o Nephrotic syndromes (see previous)
• **Postrenal**: blockage of urinary flow
o Old dude with prostatic hyperplasia
o Cancer or stones

ACUTE TUBULAR NECROSIS

• MOST COMMON cause of ARF
• Old person after MI → proximal tubules damaged by ISCHEMIA (reversible)
• Cells become flattened, lose microvilli
• U/A: proteinuria, granular casts & low urine osmolality
• Initial oliguric phase: <400cc/24 hrs; death occurs most commonly in
• Diuretic phase: usu complete recovery
• Indications for dialysis: hyerpkalemia, metabolic acidosis, pulmonary edema, pericarditis, seizures

CHRONIC RENAL FAILURE

• Irreversible, end-stage
• Causes: diabetes, HTN, glomerulonephritis
• **Uremia:**
o Azotemia (↑ BUN, creatinine)
o Acidosis
o Hyperkalemia (↑ K+)
o Abnormal fluid volume control → heart failure
o Hypocalcemia
o Anemia (↓ EPO)
o HTN (↑ renin)

CHRONIC PYELONEPHRITIS

• One entity that leads to CRF
• Fibrotic scarring of parenchyma
• Deformed pelvis & calyces
• **Thyroid kidney** (pink protein pools in tubules)

Abbreviations:
HTN = Hypertension
EPO = Erythropoietin
ARF = Acute Renal Failure
CRF = Chronic Renal Failure
U/A = Urinalysis
WBC = White blood cell